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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	PAPER NUMBER
1657	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,811	EDENS ET AL.	
	Examiner	Art Unit	
	SATYENDRA K. SINGH	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12 and 23-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12 and 23-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **06/14/2010** has been entered.

Claims 9-12 and 23-31 (as currently amended) are pending in this application.

Claims 1-8 and 13-22 have been canceled by applicants.

Claims 9-12 and 23-31 (invention of group V, elected specie "**celiac disease**") have been examined on their merits in this office action.

NOTE: Claims have been interpreted as being generally directed to **a method of treatment** of patients in need thereof or patients suffering from "celiac disease", wherein the method requires oral (i.e. administration route) ingestion of a dietary supplement comprising a proline specific endoprotease (PEP) having functional properties/characteristics as recited in instant claims.

Objections to Specification

1. The instant disclosure is objected to because it contains an **embedded hyperlink** and/or other form of browser-executable code on page 14, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicants are advised to check for such embedded hyperlink and/or other form of browser-executable code in the entire disclosure and amend accordingly. Appropriate correction is required.

2. This application contains **sequence disclosures** at pages 2, 10, 16, 23, 27, 28, 30, 32-38, and tables 1, 2, 6, 7, for examples, that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in **37 C.F.R. § 1.821(a((1) and (a)(2).** However, this application fails to comply with one or more of the requirements of 37 C.F.R. § 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences And/Or Amino Acid Sequence Disclosures". Wherein attention is directed to **paragraph(s) §1.82 (c) and (e).**

Although an examination of this application on the merits can proceed without prior compliance, compliance with the Sequence Rules is required for the response to this Office action to be complete. Applicants are advised to check the entire specification as originally filed for providing such sequence listing in compliance with the above stated sequence disclosure rules. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names **joint inventors**. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 9-12 and 23-31 (as currently amended) **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Messer et al (1976) in view of Hausch et al (2002) and Dekker et al (WO 02/45524 A2).

Claims have been interpreted as generally directed to **a method of treatment of patients in need thereof or patients suffering from celiac disease** (elected specie of disease), wherein the method requires oral (i.e. ingestion route) administration of a dietary supplement or a medicament (taken as a pharmaceutical composition) comprising a proline specific endoprotease (obtained from *Aspergillus niger*; that can hydrolyze proline-rich peptides that are associated with the occurrence of celiac disease at a pH of below 5.5, or that has a pH optimum below 6.5; and which is active in the stomach of the patient; see specific recitations of claims 9-11, as amended).

Messer et al (IDS) disclose a method of treatment of patients in need thereof or patients suffering from celiac disease, wherein the patients are orally administered a dietary formulation or supplement comprising a digestive enzyme (i.e. oral enzyme therapy to treat celiac disease; see entire report at page 1022) such as papain (in the form of enteric-coated tablets of commercially available papain) in order to help destroy the gluten to improve response to gluten free diet in the patients suffering from celiac disease, wherein based on their experimental results, they recommend oral, crude papain enzyme administration as an adjunct treatment to gluten-free diet in the treatment of gluten intolerance in patients in need thereof.

However, Messer et al do not use "**proline specific endoprotease**" that has the hydrolytic activity at **pH below 5.5, or a pH optimum of below 6.5** as required by the instant claims.

Hausch et al [U] disclose the immunodominant gliadin peptides that are now known to be the cause of celiac disease or gluten intolerance, and they show that these peptides are exceptionally resistant to enzymatic digestion in patients with such disorders as celiac disease (see abstract, and introduction, in particular). They also disclose the fact, that a trace amounts of exogenously added (both, *in vitro* or *ex vivo*) prolyl endopeptidase (albeit from a bacterial source) was able to efficiently destroy or digest said immunodominant peptides, suggesting "a possible enzyme therapy strategy for celiac sprue..." (see abstract, page G996, in particular). Hausch et al also state that "*...therefore, we suggest that supplementation of the celiac diet with bioavailable PEP, with or without DPP IV and DCP I, by virtue of facilitating gliadin peptide cleavage to nontoxic and/or digestible fragments may be useful in attenuating or perhaps even eliminating the inflammatory response to gluten. Such a strategy would be analogous to the*

enzyme therapy treatment *in the case of lactose intolerance, where orally administered lactase is effective in cleaving and thereby detoxifying the lactose in milk product*" (see page G1002, left column, and references contained therein)

Therefore, given the detailed disclosure by the cited prior art references of record, at the time this invention was made, it would have been obvious to a person of ordinary skill in the art to modify the method of treatment disclosed by Messer et al such that it uses a dietary supplement comprising prolyl endopeptidase as explicitly suggested and motivated by the disclosure of Hausch et al. Since, Hausch et al clearly demonstrated the use of prolyl endopeptidase in destroying the immunogenic gluten peptides that are known to be the root cause of the inflammatory response in patients with celiac disease, an artisan of ordinary skill in the art would be motivated to substitute the enzyme, papain with the prolyl endopeptidase of Hausch et al in order to successfully destroy the gliadin peptides, and thus achieve a superior and effective method of treatment of patients in need thereof.

However, the combined teachings of Messer et al and Hausch et al do not explicitly disclose the use of **a prolyl endoprotease that has the hydrolytic activity at pH below 5.5, or a pH optimum of below 6.5**, and that is obtained from an ***Aspergillus niger*** **sp**.

Dekker et al [N] disclose such an enzyme (a prolyl endoprotease that can hydrolyze proline-rich peptides that are associated with celiac disease at a pH of below 5.5, or that has a pH optimum below 6.5; i.e. mimicking stomach pH, and that has been derived from *Aspergillus* sp., specifically *Aspergillus niger*) that can be used for digesting or hydrolyzing various types of proteins and peptides to obtain hydrolysates that can be used in various applications, including allergen free diets for babies, and for obtaining wheat gluten hydrolysates which are normally

difficult to obtain (see Dekker et al, pages 3, 8 and 11, in particular; and claims) as it is poorly soluble at acidic pH. They disclose the extensive usefulness and application of this enzyme that acts in acidic conditions with a pH optimum below 6.5 (preferably pH 3.5 to 6.5), and that can be used to digest wheat gluten from barley into digestible peptides in order to protect gastric mucosa, which is normally at acidic pH. Thus, Dekker et al explicitly disclose a poline-specific endoprotease derived from *Aspergillus niger* that is fully active in acidic pH environment, and is not inactivated at low pH ranges such as below 6.5.

Thus, given the disclosure from Dekker et al for a suitable prolyl endoprotease (derived from *Aspergillus* sp.) that can work best under the acidic pH conditions (such as of stomach and/or intestine of patients), an artisan of ordinary skill in the art would have been motivated to substitute a better prolyl endoprotease enzyme, albeit from an *Aspergillus* sp. such as *Aspergillus niger*, as explicitly taught by the referenced invention of Dekker et al in order to achieve a superior method (using an improved enzyme, that has an acidic pH optimum, similar to the stomach environment) of treatment of patients suffering from celiac disease with a reasonable expectation of success, as evidenced by the detailed disclosure of Dekker et al that demonstrate the efficient digestion of various types of proteins using said prolyl endoprotease, albeit *in vitro*, having an acidic pH optimum (and therefore can be active in acidic environments such as mammalian stomach), which will be suitable for the enzyme therapy (in the method of Messer et al and Hausch et al) as an oral dietary supplement for hydrolyzing potentially harmful peptides in the stomach, before they reach the intestine of sensitive patients. It is noted that applicants have used the same PEP enzyme from *Aspergillus niger* sp. as specifically disclosed by Dekker et al that has all the functional characteristics such as acidic pH optimum, etc. (see instant disclosure,

page 12, line 21 through page 15, line 10) as currently recited in the claims. The invention as claimed, therefore, does not distinguish itself over the combined teachings/suggestion from the cited prior art references of record.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made.

As per MPEP 2144.06, *In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).*

As per MPEP 2111.01, *during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Response to Applicant's Arguments

Applicant's arguments filed on 06/14/2010 (as they pertain to the prior art rejection of record) have been fully considered but they are not persuasive for the following reasons of record:

First, it is noted that applicants have submitted two NPL references (Stepniak et al and Mitea et al; see remarks, pages 8-9) as evidentiary support documents. However, these references have not been submitted as proper IDS on the record, and therefore, have been considered by the examiner only to the extent as they pertain to applicant's current arguments, which are responded to hereinafter.

In response to applicant's arguments against the cited prior art references individually (see remarks, pages 6-7), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The argument that both Messer et al and Hausch et al "teach away" from the instant invention as they suggest use of "enteric coating", or use of PEP for breakdown of gliadin peptides "in the BBM or in the intestine" is not found to be persuasive because the combined disclosure of Messer et al and Hausch et al clearly provides the basis that the goal in the prior art is to "predigest" the gluten peptides (or antigenic or inflammatory peptides) before they reach patient's intestinal mucosa (where they cause inflammatory response, and therefore celiac disease, etc.), and given the disclosure of Dekker et al for the appropriate PEP enzyme (that has low pH optimum, and that can work in acidic pH environments, such as mammalian stomach) from *Aspergillus niger*, an artisan of ordinary skill in the art would have been motivated to substitute a better PEP enzyme that can work at acidic pH (and that can also be used *in vitro* to pre-digest hard to digest peptides in food products, as demonstrated by Dekker et al; see discussion above) of stomach as an enzyme therapy composition as specifically suggested by Hausch et al. The limitations of the "PEP being active in stomach" are inherent in the PEP enzyme (i.e. intrinsic functional characteristics such as pH optimum, activity, selectivity/specificity, etc.) used to pre-digest the food product, or being used in the pharmaceutical composition that is being orally administered (i.e. ingested by patient) to the subject in need thereof. The suggestions of enteric coating are given in the prior art in order to protect the oral enzyme formulations that are not resistant to acidic pH environments such as

stomach. Since, Dekker et al disclose and demonstrate the fact that a specific PEP from *Aspergillus niger* has the capability to digest "allergenic peptides" in food products under acidic pH conditions (akin to mammalian stomach), a person of ordinary skill in the art, at the time this invention was made, would have had a reasonable expectation of success in substituting and using Dekker's protease in place of the proline endoproteases used in the art (such as those in Messer et al and Hausch et al) that specifically need "enteric coating" and/or such protection.

The argument that "*...However, Dekker describes the use of proline specific endoprotease in vitro rather than in vivo. While reference is made to reducing allergenicity of food (Dekker, page 7 lines 28-32), the enzyme is incubated with the food proteins prior to consumption. It would appear that enzymes used in this way are killed off during food preparation rather than during food digestion. Dekker is irrelevant to the method as claimed*", is duly noted and fully considered. However, it is not found to be persuasive because, as noted earlier in the rejection, it is the same enzyme from Dekker et al, which is being used by applicants for the instant invention as claimed and disclosed (see instant disclosure, page 12, line 21 through page 15, line 10), and therefore, the argument that "Dekker is irrelevant to the method as claimed", is interesting, but not found to be persuasive. Also, since, Dekker et al have demonstrated the *in vitro* pre-digestion of food products, in order to achieve allergen free food products that are suitable for ingestion by sensitive subject populations that are affected by gluten peptides, it would stand an obvious reason why one of ordinary skill in the art would be motivated to use and/or substitute such a superior PEP enzyme obtained from *A. niger*, as per their disclosure and/or suggestions. The argument that the "*enzymes used in this way are killed off during food preparation rather than during food digestion*" is not found to be persuasive

because instant claim 10, for example only requires the process step of "*digesting food with said proline specific endopeptidase*", which would have been fully contemplated by an artisan of ordinary skill in the art from the disclosure of Dekker et al alone, especially for producing pre-digested food *in vitro* that are low or free in allergenic peptides such as devoid of celiac related epitopes.

The arguments of "unexpected benefits" based on the scientific publications of Stepniak et al and Mitea et al (submitted by applicants as evidence; see remarks, pages 8-9) that demonstrate "efficient gluten degradation" using the *A. niger* PEP (Stepniak et al), or demonstrate efficient digestion of toxic gluten epitopes using said PEP in a "*validated dynamic system closely matching the human gastrointestinal tract (TIM system)*" is noted and fully considered. However, such benefits arising out of the use and/or substitution of a superior enzyme (such as the PEP obtained from *A. niger* having an acidic pH optimum that can also work in acidic pH such as a mammalian stomach, as explicitly disclosed by Dekker et al) for making or using allergenic peptide-free food products that can be pre-digested with said enzyme, and/or used as an enzyme therapy or supplementation *via* an oral pharmaceutical composition (or as an medicament) for ingestion by a patient population in specific need thereof, would have been obvious and fully expected by an artisan of ordinary skill in the art, at the time of this invention, given the combined disclosures and/or suggestions of the cited prior art references of record for use of such an enzyme for efficiently degrading allergenic food products containing toxic peptides. Thus the invention as claimed does not distinguish itself over the combined teachings of the cited prior art as discussed above in the obviousness rejection of record.

Conclusion

NO claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SATYENDRA K. SINGH whose telephone number is (571)272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JON P. WEBER can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Satyendra K. Singh/
Examiner, Art Unit 1657

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657